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Experience with Surgical Excision in Childhood Pheochromocytoma

Pheochromocytoma is one of the potentially fatal causes of childhood hypertension. The study aims to analyze the results of our experiences in pheochromocytomas and the long-term results of its surgical treatment in children. The records of 15 children (11 boys, 4 girls) treated for pheochromocytoma in our unit during the period of 1984 and 2002 were reviewed retrospectively. The average age at surgery was 11.7 yr (range 6 yr 9 months–15 yr 7 months). Localized disease is defined as the cases without the invasion of surrounding tissue, regional disease as the invasion of surrounding tissue and metastatic disease as distant metastases. The mean follow-up after pheochromocytoma excision was 95 months (range 5 to 221 months). Tumors were located in the adrenal gland in 11 (bilaterally in 4) and extra-adrenally in 4. Localized disease occurred in 14 patients and regional disease in one. Only one patient was associated with von Hippel Lindau syndrome. Adrenalectomy or total excision of extra adrenal tumor was performed. Four patients (26.7%) recurred after the first operation (at 2 yr 9 months to 14 yr) and regional disease recurred in one patient three times. Early diagnosis, surgical excision, and long-term follow up are most important for the appropriate treatment of childhood pheochromocytoma.

Key Words : *Pheochromocytoma; Child; Therapy; Surgical Procedures, Operative*

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INTRODUCTION

Pheochromocytoma is rare but a critical tumor of chromaffin cells, which is frequently considered in the evaluation of hypertension, arrhythmia, or panic disorder and in the follow-up of patients with particular genetic diseases (1, 2). Pheochromocytoma is a one of the potentially fatal causes of childhood hypertension and accounts for about 1% of pediatric hypertensive patients (3, 4).

Because pheochromocytoma is more common in adults than in children, most of the data available on its behavior and management have been based on adults, and thus the etiopathogenesis and management of pediatric pheochromocytoma remains obscure (1). However, differences in the behavior of this tumor in children require special considerations to ensure optimal management of such pediatric population.

This study aims to review one of the big pediatric series ever studied at a single medical center, and to make a brief review on the literature concerning advances in the genetics, biochemical diagnosis, localization, and management of pheochromocytoma.

MATERIALS AND METHODS

Between 1984 and 2002 we treated 15 patients with pheochromocytoma: 11 males and 4 females with an average age at surgery of 11.7 yr ranging from 6 yr 9 months to 15 yr 7 months.

We retrospectively evaluated the information available on each patient, including age, sex, clinical characteristics, diagnostic methods, treatment, pathologic finding, and outcome. Tumors were localized by ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), and by MIBG scintigraphy. For some patients, intravenous pyelography (IVP) was conducted. Localized disease was defined as the case without a pathologic finding of surrounding tissue invasion, regional disease as disease with a pathologic finding of surrounding tissue invasion. Metastatic disease was defined as disease with distant metastases. The findings that are disclosed by pathologic examination are as follows: surrounding tissue invasion, capsular invasion, vascular invasion, necrosis, pleomorphism, atypical mitosis, cyst formation, and lymphoid reaction.

In this study, the mean follow-up after resection was 95 months (5-223 months). Statistical evaluations were performed using the SPSS package (chi-squre test and Fisher's exact test).

RESULTS

One patient (6.6%) only was associated with von Hippel

Lindau disease. This patient had a father with a history of pheochromocytoma, which was treated by surgical resection when he was 45 yr old.

Symptoms at presentation are listed in Table 1. The outstanding and common symptoms were sweating and hypertension. Hypertension was noted in all patients but one. Their overall mean arterial blood pressures (ABPs) were 160 mmHg ranging from 140 to 190 mmHg and 100 mmHg ranging from 70 to 120 mmHg for systolic and diastolic pressure respectively. Mean time between symptom onset and diagnosis was 11.9 months ranging from 1 month to 48 months. Abnormal electrocardiography (left ventricular hypertrophy; n=7, tachycardia; n=2, prolonged QT interval; n=4), hypertensive retinopathy (n=5), cardiomegaly at chest radiography (n=6), and hypertensive encephalopathy (n=2) were also found.

Table 1. Symptoms presented by pheochromocytoma patients

Symptom	No. of patients	%
Hypertension, paroxysmal	11	73.3
sustained	3	20
Sweating	14	93.3
Headache	9	60
Palpitation	8	53.3
Vomiting	8	53.3
Weight loss	7	46.6
Visual disturbance	6	40
Abdominal pain	6	40
Perspiration	4	26.6
Dyspnea	3	20
Anorexia	3	20
Easy fatigability	2	13.3
Chest pain	1	6.6
Loss of consciousness	1	6.6
Heat intolerance	1	6.6
Diarrhea	1	6.6
Tarchycardia	1	6.6
Seizure	1	6.6

The average 24-hr daily urinary vanillylmendelic acid (VMA) levels were 28.8 mg/24 hr (range 0.6-52.8 mg/24 hr): all patients had a value higher than the upper limit of normal range (normal value 0.7-6.9 mg/24 hr). Elevated levels of serum epinephrine were found in one of the 15 patients only, and elevated levels of norepinephrine in three. A CT scan was performed on all patients. ^{123}I-metaiodobenzylguanidine (MIBG) scintigraphy was performed in ten patients and intravenous pyelography in four. The other diagnostic methods used were abdomen ultrasonography, and renal scanning. Bone scans were performed in six patients to detect bone metastasis, and brain MRI and EEG done in two patients who appeared symptoms of hypertensive encephalopathy.

Preoperative treatment with the phenoxybenzamine, nonselective α-adrenergic antagonist, was performed in all patients for a median of 14 days (range 7-21 days). The mean dose administered was 1.4 mg/kg/day (range 0.2-2.44 mg/kg/day). Prazocine, hydralazine, nifedipine, digoxine, lasix, or propranolol was also used intermittently. Preoperative hydration was performed in 11 patients. The ABPs of all patients were controlled and no intraoperative ABP fluctuation was observed.

Table 2 shows the clinical characteristics and outcomes of surgical resection. The transperitoneal approach was adopted in all patients, as we preferred a subcostal incision. Fourteen patients had localized disease and one patient regional disease. None had metastatic disease. The tumors were in the right side adrenal gland in 3 patients, in the left side gland in 4, bilaterally in 4, and extra-adrenally in 4. Three of the four extra-adrenal pheochromocytomas were located in the organ of Zuckerkandle and one was at the left renal hilum. Seven patients with ipsilateral adrenal pheochromocytoma underwent ipsilateral adrenalectomy, including cortex sparing adrenalectomy (n=2), and contralateral adrenal gland biopsy

Table 2. Clinical characteristics and outcome

Case	Age at operation	Sex	Localization	Operation	Pathology	Outcome
1	10 yr 1 mon	F	Right adrenal	Rt. adrenalectomy	Localized	Recovery
2	10 yr 1 mon	M	Bilateral	Bilat. adrenalectomy	Localized	Recovery
3	13 yr 6 mon	M	Extra adrenal	Mass excision	Localized	Recurrence
4	6 yr 9 mon	M	Extra adrenal	Mass excision	Regional	Recurrence
5	15 yr 7 mon	M	Left adrenal	Lt. adrenalectomy†	Localized	Recovery
6	12 yr 4 mon	M	Bilateral	Bilat. adrenalectomy	Localized	Recurrence
7	14 yr	F	Extra adrenal	Mass excision	Localized	Recovery
8	8 yr 5 mon	M	Left adrenal	Lt. adrenalectomy	Localized	Recovery
9	12 yr 7 mon	F	Bilateral	Bilat. adrenalectomy	Localized	Recurrence
10	13 yr 1 mon	M	Left adrenal	Lt. adrenalectomy† + rt. biopsy	Localized	Recovery
11	10 yr 6 mon	M	Extra adrenal	Mass excision	Localized	Recovery
12	12 yr 11 mon	M	Right adrenal	Rt. adrenalectomy	Localized	Recovery
13	14 yr 3 mon	M	Right adrenal	Rt. adrenalectomy	Localized	Recovery
14	11 yr 2 mon	F	Left adrenal	Lt. adrenalectomy	Localized	Recovery
15*	10 yr 3 mon	M	Bilateral	Bilat. adrenalectomy†	Localized	Recovery

*: Family history of pheochromocytoma (his father), †: Cortex sparing adrenalectomy.

(n=1). Four patients with bilateral pheochromocytoma underwent bilateral adrenalectomy, including cortex-sparing adrenalectomy (n=1). Four patients with an extra-adrenal pheochromocytoma received total excision, which included ipsilateral nephrectomy in one case with regional disease. The mean size of the removed masses was 4 cm ranging from 1.2 to 6 cm.

After surgery, thirteen of the 15 patients became normotensive state without hypertension medication. However, two patients required medical therapy for satisfactory control of blood pressure. There were several complications including operation site bleeding, ureter injury, lugol induced hypothyroidism and hypocortisonism. All complications were resolved without sequelae (Table 3). No operative mortality occurred in our series.

There was no difference of these pathologic results between recurred and non-recurred cases or between regional disease and localized disease (Table 4).

The mean follow up period to date is 95 months (5-223 months).

After tumor removal, four patients recurred with the duration range of 2 yr 9 months to 14 yr; three patients with localized disease and one patient with regional disease (Table 5). The recurrent sites include lung parenchyme, pancreas, adrenalectomy site, and the organ of Zukerkandle. One patient with recurrence in lung received wedge resection and have no recurrence. One patient with pancreatic recurrence was given MIBG therapy and was lost to follow up later. One patient with bilateral adrenalectomy site recurrence also received MIBG therapy and subsequently mass excision for hypertension control but expired due to hypertensive encephalopathy. Thus, MIBG therapy was administered to two recurred patients but its effect was meager. Of the four recurrent cases, one patient with regional disease had three separate recurrences. The first and second recurrent masses were surgically excised but the third recurrent mass has been kept under observation with anti-hypertensive medication, without surgical excision.

Table 3. Postoperative complication

Complication	No. of patients (%)	Treatment
Bleeding	1 (6.6)	Operation
Ureter injury	1 (6.6)	Primary repair
Lugol induced hypothyroidism	1 (6.6)	Oral medication
Hypocortisonism	1 (6.6)	Oral medication

DISCUSSION

Rare as it is, pheochromocytoma is a chromaffin cell tumor that must be considered in patients with hypertension, autonomic disturbances, panic attacks, adrenal incidentalomas, or familial disease featuring a predisposition to develop pheochromocytoma (1, 2). About 5-20% of these extremely rare tumor are found in the pediatric population, and with an incidence of two per million, pheochromocytoma accounts for secondary hypertension in 0.5% of children, and is more common in preadolescent boys and teenage girls (3-6).

There are some differences in behavior of pheochromocytoma between the pediatric and adult populations. Most studies have confirmed male preponderance and greater tendency for familial occurrence and multi-focality (43% in children vs. 30% in adults), an increased incidence of extra-adrenal tumors (30-40% in children vs. 10% in adults), and similar/lower risks of a malignant pheochromocytoma (3.5%) (7, 8). Our experience revealed a male predominance (73%), a preadolescent tendency (mean age: 11.7 yr), an extra-adrenal location

Table 4. Analysis of pathologic factors influencing recurrence

Pathologic factor		No. of patients	*p*-value
Surrounding tissue invasion	(+)	2	0.164
	(−)	17	
Capsular invasion	(+)	7	0.297
	(−)	12	
Vascular invasion	(+)	0	NA
	(−)	19	
Necrosis	(+)	2	0.322
	(−)	17	
Pleomorphism	Mild	10	0.255
	Moderate	9	
Atypical mitosis	(+)	0	NA
	(−)	19	
Cyst formation	(+)	2	0.322
	(−)	17	
Lymphoid reaction	(+)	2	0.678
	(−)	17	

Table 5. Recurrent cases after pheochromocytoma resection

Case	Localization	1st operation	Recurrence Interval	Recurrence site	Treatment	F/U (After recurrence)	Outcome
3	Extraadrenal	Mass excision	14 yr	Chest LLL, RLL	Excision (VATS)	4 yr 7 mon	Recovery
4	Extraadrenal	Mass excision	1. 8 yr 3 mon	1. Extraadarenal	1. Excision		Extradarenal mass
			2. 10 yr 3 mon	2. Extraadarenal	2. Excision		Medication
			3. 13 yr	3. Extraadarenal	3. Observation	1 yr 1 mon	(antihypertensive)
6	Bilateral	Bilat. Adrenalectomy	6 yr 3 mon	Pancreas head and tail	MIBG therapy	F/U loss	F/U loss
9	Bilateral	Bilat. Adrenalectomy	2 yr 9 mon	Bilat. adrenal gland site	MIBG therapy + Mass excision	8 yr 6 mon	Expired

tendency (26.6%), and lower malignant development (0%), but the incidence of multifocal locations (26.6%). And a familial tendency (6.6%) was lower than that found in the literatures (7, 8).

The presentation of pheochromocytoma is variable, and patients may often be asymptomatic (9). Children most commonly present with signs and symptoms related to hypertension including headache. Some symptoms of pheochromocytoma include sweating, visual complaints, nausea, vomiting, weight loss, polydipsia and polyuria and these are more common in children than in adults (7, 10). In our series, symptoms such as hypertension, sweating, headache, palpitations and vomiting tended to agree with findings commonly presented in the literature. Although children with pheochromocytoma usually present with sustained hypertension, 80% of our patients presented with paroxysmal hypertension.

The most important consideration when choosing an initial biochemical test is the reliability of the test in terms of excluding pheochromocytoma. The diagnosis of pheochromocytoma usually requires biochemical data indicating excessive catecholamine production by the tumor, which is performed by measuring vanillylmendelic acid (VMA) and metanephrine 24-hr urinary excretion, giving a sensitivity and specificity of 80-100% (10-13). A positive correlation between the size of a tumor and the urinary VMA level has been reported (10). In our series, all patients had an elevated level of urine VMA, but we cannot confirm a positive correlation between tumor size and the urinary VMA level ($p>0.05$). Further advances, measurements of plasma free metanephrines, normetanephrine, metanephrine, and the respective *o*-methylated metabolites of NE or epinephrine represent recently developed. This development is helpful for the diagnosis of pheochromocytoma (11, 12).

Preoperative imaging procedures are essential to the accurate and noninvasive localization of the number, site, size, and extension of these lesions for successful surgical management. In a recent study of 282 patients in which MR imaging, CT, and MIBG were compared, MR imaging was found to be the most sensitive technique for localization of adrenal and extra-adrenal pheochromocytomas. Computed tomography and magnetic resonance imaging have less than ideal sensitivities. ^{131}I-metaiodobenzylguanidine (MIBG) scanning and positron emission tomography have been used in identifying primary, recurrent and metastatic tumors (2, 7). CT and/or ultrasonography were used in all patients and allowed the visualization of the tumor site, the tumor size and of tumor extension. MIBG scanning was also used to detect recurrent and metastatic tumors in 10 patients and recurrent tumor were detected in four patients.

The most important aspect of preoperative preparation is the identification and treatment of hypertension and of other sequelae of catecholamine-induced vasoconstriction. Most centers support to place patients on adrenergic blockades such as phenoxybenzamine and upon a positive fluid balance preoperatively (2, 7, 13-16). Current guidelines recommend phenoxybenzamine dosages of 160 mg at the maximum per day, divided into four equal doses every 6 hr, which should be gradually tapered over a 10- to 14-day period (13).

Surgical excision of pheochromocytoma has been performed using a transabdominal approach, with palpation of the contralateral adrenal gland and sympathetic chain to detect additional tumors (2). Compared to open operations, laparoscopic surgery has the advantages of less postoperative pain, reduced postoperative stay, and a reduced need for analgesics and of improved functional and cosmetic results. Therefore, laparoscopic surgery is associated with reduced morbidity versus open surgery in experienced hands (2, 6, 7, 14, 17-21). Despite many adult studies, few reports have described the results of this laparoscopic technique in pediatric patients, and more data is needed to confirm benefits of the laparoscopic approach in pediatric patients.

Because recurrent pheochromocytomas may develop by 20% to 33% of patients with familial syndrome undergoing partial adrenalectomy, bilateral adrenalectomy is recommended in bilateral pheochromocytoma, especially associated with hereditary syndromes. However, the range of 25% and 33% of patients undergoing bilateral adrenalectomy develop adisonism crisis at certain point of time, and the attendant mortality rates are high. Moreover, 30% of patients develop clinically significant fatigue, and 48% consider themselves handicapped (22, 23). Therefore, a minimally invasive approach, such as bilateral adrenal cortex-sparing tumor enucleation, certainly presents as an intriguing alternative to bilateral adrenalectomy, especially in those associated with hereditary syndromes. Given the greater likelihood of a metachronous recurrence in children, consideration should be given adrenal-sparing surgery in selected patients (2, 7, 13). We performed cortex-sparing adrenalectomy in two ipsilateral adrenal pheochromocytomas and in one bilateral adrenal pheochromocytoma. The three patients that underwent cortex-sparing adrenalectomy survived without recurrence or hypocortisonism (follow-up periods: 13 yr 5 months, 11 yr 5 months, and 5 months), but we were not able to confirm a significant difference between the cortex spared adrenalectomy group and the cortex no-spared adrenalectomy group in terms of the postoperative cortisol level.

Malignant pheochromocytoma is rare in childhood and the prognosis of this tumor in children is not well known. Presenting signs, the localizations of the primary tumor or of metastases, and the course of malignant pheochromocytoma in children do not seem to be significantly different from those in adults (24). In cases of malignant pheochromocytoma, multimodality treatments can be used. However, the benefits of chemotherapy, ^{131}I-MIBG therapy, external radiation and octreotide remained undetermined. The mean 5-yr survival rate for malignant pheochromocytomas is about 40% (13, 24).

Ten percent of pheochromocytoma are associated with familial cancer syndromes, such as multiple endocrine neoplasm

type 2, von Hippel-Lindau, neurofibromatosis type 1, and familial carotid body tumors in which germ-line mutation of the *RET*, *VHL*, or *NF1* genes have been found (2, 6, 7). Patients with a positive family history, bilateral adrenal pheochromocytoma, recurrent or multiple pheochromocytoma, and symptoms at a younger age should undergo clinical or genetic testing mutations of the von Hippel-Lindau or *RET* genes. Succinate dehydrogenase mutation has been described previously in five families with familial paraganglioma syndrome (25-27). In both the sporadic and familial forms of pheochromocytoma, allelic losses at 1p, 3p, 17p, and 22q have been reported, yet the molecular pathogenesis of these tumors is largely unknown (28). In one patient with familial pheochromocytoma, the *VHL* genes were positive.

Recurrence in pheochromocytoma has been reported to range from 10% to 40% (10, 29-31), which concurs with our recurrence rate (26.6%). In the current study, recurrence occurred in three patients with localized tumors and in one with regional tumors. However no significant difference was observed between localized and regional tumors in this regard. In three of four patients with recurrence, surgical resection has produced good results in terms of the relief of hypertension, but MIBG therapy, which was performed for 2 patients, has produced no symptom relief.

Our conclusion is that early diagnosis and total excision constitute proper management in pheochromocytoma, and that the treatment of choice in recurred pheochromocytoma is surgical excision, if possible. Furthermore, since the interval between resection and recurrence varies, long-term follow-up should be performed in pediatric pheochromocytoma.

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